ORIGINAL ARTICLE VIROLOGY

Use of efavirenz or atazanavir/ritonavir is associated with better clinical outcomes of HAART compared to other protease inhibitors: routine evidence from the Italian MASTER Cohort

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Abstract

Randomized trials and observational cohorts reported higher rates of virological suppression after highly active antiretroviral therapy (HAART) including efavirenz (EFV), compared with boosted protease inhibitors (PIs). Correlations with immunological and clinical outcomes are unclear. Patients of the Italian MASTER cohort who started HAART from 2000 to 2010 were selected. Outstanding outcome (composite outcome for success (COS)) was introduced. We evaluated predictors of COS (no AIDS *plus* CD4+ count >500/mm^3 *plus* HIV-RNA <500 copies/mL) and of eight single outcomes either at month 6 or at year 3. Multivariable logistic regression was conducted. There were 6259 patients selected. Patients on EFV (43%) were younger, had greater CD4+ count, presented with AIDS less frequently, and more were Italians. At year 3, 90% of patients had HIV RNA <500 copies/mL, but only 41.4% were prescribed EFV, vs. 34.1% prescribed boosted PIs achieved COS (p <0.0001). At multivariable analysis, patients on lopinavir/ritonavir had an odds ratio of 0.70 for COS at year 3 (p <0.0001). Foreign origin and positive hepatitis C virus-Ab were independently associated with worse outcome (OR 0.54, p <0.0001 and OR 0.70, p 0.01, respectively). Patients on boosted PIs developed AIDS more frequently either at month 6 (13.8% vs. 7.6%, p <0.0001) or at year 3 (17.1% vs. 13.8%, p <0.0001). At year 3, deaths of patients starting EFV were 3%, vs. 5% on boosted PIs (p 0.008). In this study, naïve patients on EFV performed better than those on boosted PIs after adjustment for imbalances at baseline. Even when virological control is achieved, COS is relatively rare. Hepatitis C virus-positive patients and those of foreign origin are at risk of not obtaining COS.

Keywords: AIDS events, composite outcome, deaths, first-line therapy, immunological response, non-nucleoside reverse transcriptase inhibitors, ritonavir-boosted protease inhibitors, virological response
Original Submission: 2 July 2014; **Revised Submission:** 8 October 2014; **Accepted:** 23 October 2014
Editor: G. Antonelli
Article published online: 11 November 2014

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Introduction

The 2014 guidelines for management of human immunodeficiency virus (HIV) infection recommended highly active antiretroviral therapy (HAART), including two nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs) as backbone, associated with a non-nucleoside reverse

http://dx.doi.org/10.1016/j.cmi.2014.10.022

transcriptase inhibitor (NNRTI), a ritonavir-boosted protease inhibitor (PI/r), or an integrase strand transfer inhibitor as anchor drugs [1].

Although not invariably [2,3], randomized clinical trials reported higher rates of virological suppression with NNRTIs as compared to boosted PIs [4–7]. Some observational studies confirmed higher rates of virological success after efavirenz (EFV) initiation when compared with boosted PIs [8–10], whilst other cohort studies did not reveal marked differences in terms of virological end points [11–13]. However, boosted PIs may perform better than EFV when immunological success rates were considered [10]. Also, reported rates of AIDS events and deaths were similar for patients treated with either EFV or boosted PIs in observational cohort studies [11–13].

Even more controversial results were obtained when comparing different boosted PIs. For instance, in a recent trial, a similar incidence of virological failures has been reported at week 96, although treatment discontinuations of therapy occurred more frequently in patients on atazanavir boosted by ritonavir (ATV/r) (14%) than in those on darunavir/r (DRV/r) (5%) [14]. Nonetheless, randomized clinical trials are often unable or unpowered to relate results of viro-immunological responses with clinical outcomes.

This study aimed at comparing rates of death, AIDS events, non-AIDS events, changes of anchor drugs, virological suppression, and immunological response among patients treated with EFV or boosted PIs in first line and to analyse predictors of the clinical response. In addition to single/separate end points [8–12], this study evaluated composite outcomes, which included at the same time CD4+ T cell count, viral load, and AIDS events, both at mid-term (3 years) and at short-term (6 months) follow-up.

Methods

The MASTER is a multi-centre cohort study that involves 10 major Italian centres for HIV care. Data of HIV-infected patients from each of these centres are collected, revised, and shared with periodic updates using a common electronic database (Health & Notes 3.5®, Healthware S.p.A., Naples, Italy), creating a large longitudinal observational cohort of 24 814 patients as of January 2013.

In this study, HIV-infected adults who started a first-line HAART from January 1 2000 to December 31, 2010 were selected. HAART had to include two N(t)RTIs as backbone, and a boosted PI or EFV as anchor drugs (no other NNRTIs were considered). Prescribed PIs were DRV, lopinavir (LPV) or ATV, all boosted with ritonavir (r). Patients were divided into two groups by class of anchor drug (EFV vs. boosted PI).

Patient baseline characteristics were collected according to time of first-line therapy (searching for the most recent measure up to 90 days prior to treatment initiation). The following characteristics were considered: age, calendar year, gender, mode of HIV transmission, nationality, hepatitis co-infection (hepatitis C virus antibody (HCV-Ab) and/or hepatitis B surface antigen (HBsAg) positivity), HIV RNA load (expressed as $\log_{10}$ copies/mL), CD4+ T cell count, CD4+ T cell percentage, HAART backbone, type of anchor drug (EFV or boosted PI), any prior AIDS-defining event and time from HIV diagnosis to baseline. Date of the latest follow-up, death, and stopping date of anchor drugs were also reported.

The first evaluation of outcomes was fixed at month 6 from baseline. At this time point, HIV RNA, CD4+ T cell count, death, and any AIDS or non-AIDS events were collected closer to month 6 and after at least 90 days from baseline.

Second follow-up was fixed at year 3. The same set of variables was considered, all closer to year 3 and collected after at least 2 years from baseline.

Eight single binary outcomes were defined and assessed at each time point: HIV RNA below 500 copies/mL, CD4+ T cells below 350/mm^3, CD4+ T cells below 500/mm^3, AIDS event, non-AIDS event, death for any cause, change of the anchor drug, and status of the follow-up (continuing or interrupted). The 500 copies/mL cut-off for HIV RNA was chosen to avoid possible bias related to disparities in the use of ultrasensitive tests that occurred after the beginning of this study. In addition, two composite outcomes defining clinical success and one composite outcome defining clinical failure were defined. Although the use of composite outcomes may be misleading because in many cases it is difficult to discriminate between results applied to the individual components of the outcome (for which we also analysed these individual components), clinical trials are employing these outcomes in the HIV field [15]. The first composite outcome for success (COS) included no AIDS events *plus* CD4+ T cell count above 500/mm^3 *plus* HIV RNA below 500 copies/mL. The second one included the same variables *plus* continuing the initial drug used as anchor. Composite outcome for failure included any AIDS event or death *plus* CD4+ T cell count below 500/mm^3 *plus* HIV RNA $\geq$500 copies/mL. All outcomes were evaluated either at short term or at mid term. The analysis was conducted for the above outcomes, ignoring changes of the backbone drugs. Only patients observed at each time point contributed data in the analysis.

Appropriate statistical methods were used: descriptive stratified statistics, χ^2 on cross tabulations, Wilcoxon rank-sum tests, Student's *t* tests, multivariable logistic regression (adjusting for all baseline variables), and calculation of area under the receiver operating characteristics curve to evaluate

performances of models [16] on selected outcomes. A supplementary, explorative analysis was performed for immunological, virological, and clinical end points at mid term, including univariable and multivariable logistic regression with all the above and number/reasons of the drug switches (any) as variables. Since the analysis was aimed at investigating the outcomes in those with observed data at fixed time points, in line with our previous study [10], a survival analysis was not performed. This has the drawback of ignoring outcomes occurring before the pre-defined time points. To address this issue, we performed analyses that included outcomes occurring before the stated time points and also that included patients lost to that specific end point (e.g. missing a required measure for calculating the outcome) by assigning them to one or the other class (results provided in the Supplementary Material).

Results

Patient characteristics

Overall, 6259 patients were included in this study. Patients starting boosted PIs (57%) outnumbered those initiating EFV (43%). Among patients treated with boosted PIs, 63.3% were prescribed LPV/r, 27.1% ATV/r, and 9.4% DRV/r. Italian patients were 74%, males 73%, intravenous drugs users 13.3%, homosexuals 20.6%, and heterosexuals 42.9%. Eighteen per cent of patients had at least one AIDS event reported prior to or at baseline. HBsAg carriers accounted for 15% of cases on EFV and for 20.5% on boosted PIs. Positivity for HCV-Ab accounted for 18% of patients in the EFV group and for 19.2% in the boosted PI group. As compared to patients on boosted PIs, those on EFV were younger (mean: 39.6 vs. 40.1 years; p 0.0027), had higher CD4+ T cell count (mean: 266 vs. 233 cells/mm^3, p <0.0001), fewer had AIDS events before HAART initiation (16% vs. 19.5%, p 0.0003), and were more frequently Italians (82% vs. 80, p 0.0279) (Table 1).

Outcomes

Figure 1 summarizes single and composite outcomes at month 6 (panel a) and at year 3 (panel b). Charts are stratified by type of anchor drug prescribed.

Ninety per cent of patients had an HIV-RNA load <500 copies/mL at month 6 (91% in the EFV group, 89.5% in the boosted PI group (p <0.0001)). HIV RNA <500 copies/mL was found in 90.3% of patients at year 3 (91.3% in the EFV group, 89.4% in the boosted PI group (p 0.0587)). When looking at the immunological outcome, 44.1% of patients had CD4+ T cells above 500/mm^3 at year 3 (47.8% in the EFV group, 40.6% on boosted PI (p <0.0001)).

AIDS-related events occurred more frequently in the boosted PI group than in the EFV group, both at month 6 (13.8% vs. 7.6%, p <0.0001) and at year 3 (17.1% vs. 13.8%, p

TABLE 1. Characteristics of population at baseline

	EFV (n = 2695)	Boosted PI (n = 3564)	Total (n = 6259)	p
Qualitative variables				
Gender				
Female	601 (22.3%)	1006 (28.3%)	1607 (25.7%)	<0.0001
Male	2094 (77.7%)	2558 (71.7%)	4652 (74.3%)	
HBsAg				
Negativity/unknown	2287 (84.8%)	2834 (79.5%)	5121 (81.8%)	<0.0001
Positivity	408 (15.2%)	730 (20.5%)	1138 (18.2%)	
HCV-Ab				
Negativity/unknown	2216 (82.2%)	2879 (80.8%)	5095 (81.4)	0.149
Positivity	479 (17.8%)	685 (19.2%)	1164 (18.6%)	
Nationality				
Italian	2209 (81.9%)	2842 (79.7%)	5051 (80.7%)	0.0279
Non-Italian/unknown	486 (18.1%)	722 (20.3%)	1208 (19.3%)	
Risk factor				
Heterosexual	1209 (44.9%)	1474 (41.3%)	2683 (42.9%)	<0.0001
Homosexual	657 (24.4%)	637 (17.9%)	1294 (20.6%)	
IVDU	343 (12.7%)	490 (13.7%)	833 (13.3%)	
Other/unknown	486 (18%)	963 (27.1%)	1449 (23.1%)	
AIDS events				
No	2263 (83.9%)	2866 (80.4%)	5129 (81.9%)	0.0003
Yes	432 (16.1%)	698 (19.6%)	1130 (18.0%)	
Quantitative variables, mean (*SD*)				
Age	39.64 (10.05)	40.41 (10.27)	40.08 (10.18)	0.0027
CD4+ T cells/mm^3 [a]	265.96 (179.00)	232.78 (92.44)	247.38 (187.35)	<0.0001
CD4+ T cells %[b]	15.98 (8.50)	15.46 (9.86)	15.69 (9.28)	0.04778
Log_{10} HIV RNA copies/mL[c]	4.39 (1.04)	4.42 (1.08)	4.41 (1.06)	0.2618
Calendar year	2006.26 (3.59)	2007.53 (2.97)	2006.99 (3.3)	<0.0001

p Value is expressed as result of *t*-test (age and log_{10} HIV-RNA load), Wilcoxon test (other numeric variables) or Fisher test (discrete variables).
EFV, efavirenz; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; HIV, human immunodeficiency virus; IVDU, intravenous drugs users; PI, protease inhibitor.
[a]Patients observed: 5285.
[b]Patients observed: 4908.
[c]Patients observed: 5233.

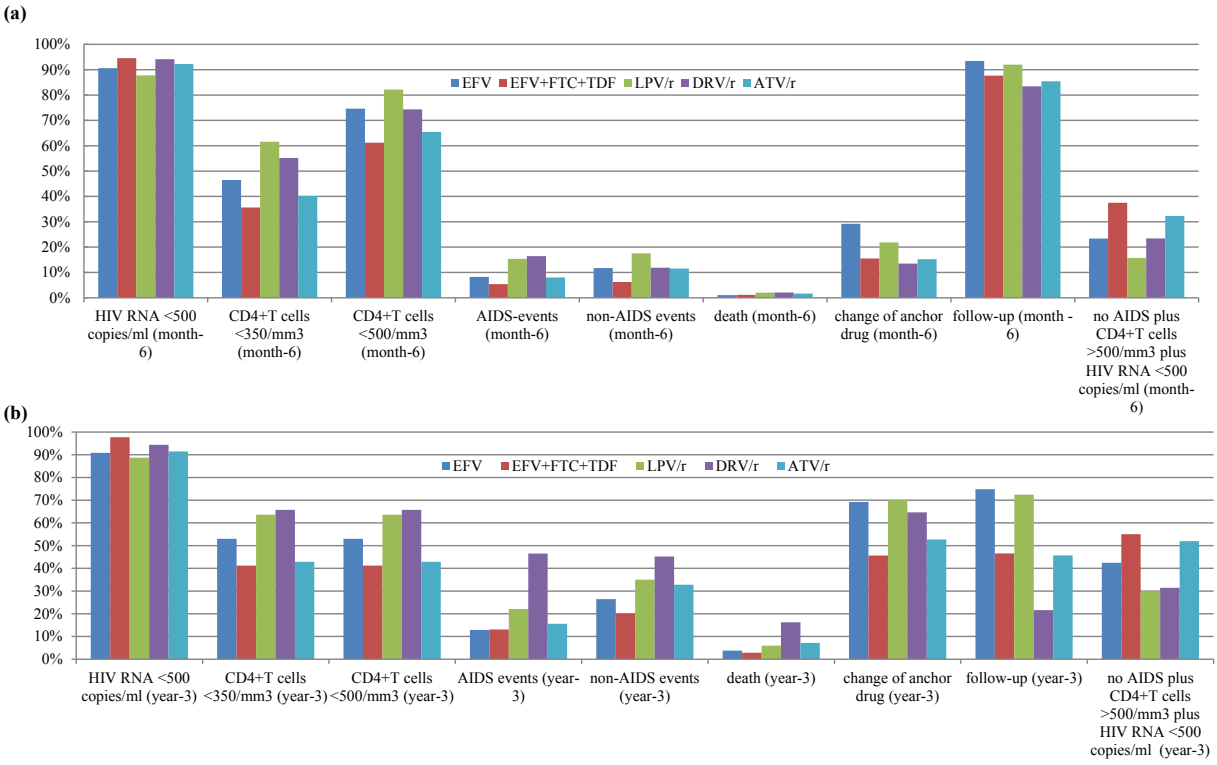

FIG. 1. Selected unadjusted outcomes (%) at (a) month 6 and at (B) year 3. ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; EFV, efavirenz; EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir (co-formulated); LPV/r, lopinavir/ritonavir.

<0.0001). At year 3, deaths in the EFV group were 3%, vs. 5% in the boosted PI group (p 0.008).

Change of anchor drugs occurred in 27.8% of patients starting EFV and in 19.3% of patients starting boosted PIs at month 6, increasing to 67.5% and 66%, respectively, at year 3 (p <0.001). COS was achieved by 22.6% of patients at month 6 (24.8% EFV, 20.8% boosted PIs (p 0.0011)), and by 38.7% of patients observed at year 3 (41.4% EFV and 34.1% boosted PIs (p <0.0001)).

Predictors of composite outcome of success

Table 2 reports univariable and multivariable logistic regression analyses for COS either at month 6 or at year 3.

In details, patients who started HAART more recently had higher odds to reach COS at year 3 (OR 1.09 per increasing calendar year, 95% CI 1.04–1.14, p <0.0001), whilst older patients had lower odds (OR 0.85, 95% CI 0.78–0.92, p <0.0001). Foreign origin was associated with a decreased probability of obtaining COS either at short (OR 0.64, 95% CI 0.50–0.82, p 0.0004) or at mid term (OR 0.67, 95% CI 0.54–0.84, p 0.0004). Positivity for HCV-Ab was also associated with a lower probability of obtaining COS at year 3 (OR 0.66, 95% CI 0.51–0.84, p 0.0008), but this association was not significant at month 6. AIDS events at baseline were associated with a lower risk of reaching COS either at month 6 (OR 0.50, 95% CI 0.36–0.68, p <0.0001) or at year 3 (OR 0.63, 95% CI 0.51–0.78, p <0.0001). As expected, patients with a CD4+T cell count at baseline >200 cells/mm^3 showed a higher probability of reaching COS, either at short or at mid term.

Patients who started LPV/r showed an OR of COS of 0.70 (95% CI 0.58–0.85, p 0.0002) when compared to patients on EFV at year 3. Instead, differences among anchor drugs could not be found significant at the 0.05 level at month 6.

Predictors of single outcomes

Probability of virological success was decreased in foreign patients compared to Italian patients, either at month 6 (OR 0.54, 95% CI 0.42–0.70, p <0.0001) or at year 3 (OR 0.61, 95% CI 0.45–0.82, p 0.0013). Likewise, in terms of immunological response, foreign origin was associated with a decreased probability of reaching CD4+ T cell count above 500/mm^3 either at short term (OR 1.53, 95% CI 1.20–1.94, p 0.0006) or at mid term (OR 1.67, 95% CI 1.34–2.07, p <0.0001). Patients on EFV had a significant increased risk of changing anchor drugs at month 6 than those on boosted PIs (for LPV/r: OR 0.59, 95% CI 0.51–0.69, p <0.0001; for DRV/r: OR 0.24, 95% CI 0.17–0.35, p <0.0001, and for ATV/r: OR 0.31, 95% CI 0.25–0.39, p <0.0001)).

TABLE 2. Composite outcome for success (COS) at month 6 and at year 3 (no AIDS events *plus* CD4+ T cell counts above 500/mm^3 *plus* HIV RNA below 500 copies/mL)

	Univariable analysis at month six		Multivariable analysis at month six		Univariable analysis at year three		Multivariable analysis at year three	
Variables	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Calendar year	1.14 (1.11–1.17)	<0.0001	1.12 (1.07–1.17)	<0.0001	1.14 (1.11–1.17)	<0.0001	1.09 (1.04–1.14)	0.0004
EFV/TDF/FTC vs. EFV	1.97 (1.46–2.64)	<0.0001	—	—	1.66 (1.16–2.38)	0.0058	—	—
LPV/r vs. EFV	0.61 (0.52–0.73)	<0.0001	—	—	0.58 (0.50–0.67)	<0.0001	0.72 (0.60–0.87)	0.0006
DRV/r vs. EFV	1.00 (0.74–1.36)	0.9867	—	—	0.62 (0.37–1.04)	0.0700	0.53 (0.29–0.97)	0.0392
ATV/r vs. EFV	1.56 (1.29–1.89)	<0.0001	—	—	1.47 (1.18–1.82)	0.0005	—	—
3TC-AZT vs. 3TC-ABC	0.86 (0.65–1.14)	0.2855	—	—	0.63 (0.49–0.82)	0.0006	—	—
3TC-D4T vs. 3TC-ABC	0.31 (0.17–0.55)	<0.0001	—	—	0.45 (0.30–0.69)	0.0002	—	—
3TC-DDI vs. 3TC-ABC	0.91 (0.62–1.34)	0.6213	1.67 (1.02–2.74)	0.0411	0.72 (0.51–1.03)	0.0715	—	—
3TC-TDF vs. 3TC-ABC	0.69 (0.47–1.01)	0.0562	—	—	0.68 (0.49–0.94)	−0.0205	—	—
ABC-DDI vs. 3TC-ABC	0.84 (0.42–1.68)	0.6161	—	—	1.01 (0.56–1.83)	0.9763	—	—
AZT-TDF vs. 3TC-ABC	0.68 (0.33–1.40)	0.2973	—	—	0.63 (0.34–1.17)	0.1447	0.50 (0.25–1.00)	0.0501
D4T-DDI vs. 3TC-ABC	0.12 (0.02–0.86)	0.0347	—	—	0.29 (0.11–0.77)	0.0133	—	—
DDI-TDF vs. 3TC-ABC	0.54 (0.20–1.43)	0.2134	—	—	0.55 (0.26–1.18)	0.1268	—	—
FTC-TDF vs. 3TC-ABC	1.11 (0.86–1.42)	0.4246	—	—	1.17 (0.92–1.50)	0.2005	—	—
Other backbone vs. 3TC-ABC	1.79 (1.26–2.54)	0.0012	—	—	1.29 (0.88–1.90)	0.1963	—	—
Age	0.76 (0.71–0.82)	<0.0001	0.83 (0.76–0.91)	<0.0001	0.82 (0.76–0.88)	<0.0001	0.84 (0.78–0.92)	<0.0001
Gender male vs. female	0.89 (0.76–1.04)	0.1370	—	—	0.93 (0.80–1.08)	0.3293	—	—
Non-Italian/unknown nationality	0.78 (0.65–0.94)	0.0097	0.64 (0.50–0.82)	0.0004	0.76 (0.63–0.91)	0.0033	0.67 (0.53–0.83)	0.0003
Homosexual vs. heterosexual	1.45 (1.22–1.72)	<0.0001	—	—	1.54 (1.31–1.82)	<0.0001	—	—
Injection drug user vs. heterosexual	0.81 (0.64–1.03)	0.0808	—	—	0.87 (0.70–1.07)	0.1821	—	—
Other/unknown risk factor vs. heterosexual	1.25 (1.04–1.50)	0.0177	—	—	1.09 (0.90–1.32)	0.3635	—	—
CD4+T cells 200 - 350 vs. <200 cells/mm^3	13.17 (9.51–18.25)	<0.0001	10.79 (7.66–15.22)	<0.0001	6.08 (5.08–7.27)	<0.0001	5.02 (4.09–6.17)	<0.0001
CD4+T cells 350 -500 vs. <200 cells/mm^3	47.26 (33.78–66.13)	<0.0001	41.81 (29.12–60.02)	<0.0001	9.10 7.23–11.45	<0.0001	7.85 (6.04–10.19)	<0.0001
CD4+ T cells >500 vs. <200 cells/mm^3	135.70 (91.29–201.71)	<0.0001	148.61 (96.62–228.57)	<0.0001	8.61 6.28–11.81	<0.0001	8.69 (6.11–12.36)	<0.0001
CD4+ T cells unknown vs. <200 cells/mm^3	9.99 (6.57–15.20)	<0.0001	9.32 (5.07–17.14)	<0.0001	2.41 1.86–3.12	<0.0001	2.69 (1.68–4.30)	<0.0001
HIV-RNA load 500–5000 vs. <500 copies/mL	0.94 (0.73–1.22)	0.6497	—		1.04 0.79–1.37	0.7714	—	—
HIV-RNA load 5000–50 000 vs. <500 copies/mL	0.89 (0.72–1.12)	0.3251	1.68 (1.26–2.24)	0.0004	1.12 0.88–1.41	0.3524	—	—
HIV-RNA load >50 000 vs. <500 copies/mL	0.65 (0.53–0.80)	<0.0001	2.57 (1.94–3.40)	<0.0001	0.90 (0.73–1.11)	0.3272	1.88 (1.45–2.44)	<0.0001
HIV-RNA load unknown vs. <500 copies/mL	0.63 (0.46–0.88)	0.0057	1.99 (1.12–3.54)	0.0185	0.70 (0.53–0.92)	0.0104	—	—
HBsAg positive vs. negative	0.84 (0.70–1.00)	0.0567	—	—	0.96 (0.82–1.14)	0.6670	1.23 (1.01–1.50)	0.0371
HCV-Ab positive vs. negative	0.83 (0.69–1.00)	0.0498	—	—	0.69 (0.58–0.82)	<0.0001	0.68 (0.53–0.87)	0.0019
Time from infection to baseline > 2 years vs. <6 months	2.24 (1.90–2.64)	<0.0001	1.28 (1.04–1.58)	0.0190	2.20 (1.87–2.58)	<0.0001	1.37 (1.13–1.66)	0.0013
Time from infection to baseline 6 months–2 years vs. <6 months	2.70 (2.23–3.26)	<0.0001	1.33 (1.05–1.68)	0.0170	2.72 (2.24–3.30)	<0.0001	1.45 (1.15–1.81)	0.0014
Time from infection–baseline unknown vs. <6 months	2.48 (1.70–3.61)	<0.0001	—	—	1.42 (0.55–3.69)	0.4670	—	—
AIDS events	0.23 (0.18–0.30)	<0.0001	0.50 (0.36–0.68)	<0.0001	0.36 (0.30–0.44)	<0.0001	0.65 (0.52–0.80)	<0.0001
Number of switches in the follow-up	0.92 (0.90–0.95)	<0.0001	0.96 (0.92–1.00)	0.0680	0.88 (0.86–0.91)	<0.0001	0.88 (0.85–0.91)	<0.0001

ABC, abacavir; ATV/r, atazanavir/ritonavir, AZT, zidovudine; DDI, didanosine; DRV/r, darunavir/ritonavir; D4T, stavudine; EFV, efavirenz; EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir (co-formulated); HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibody; HIV, human immunodeficiency virus; LPV/r, lopinavir/ritonavir; TDF, tenofovir; 3TC, lamivudine.

Variations on outcome definition, predictors, and inclusion criteria

Fifty-eight per cent of patients (n = 3625) switched to other regimens at year 3 (46% after initial EFV and 54% after boosted PIs; 16% of patients for toxicity and 6% for virological failure). Reasons and number of switches were included in the multivariable analysis for outcomes at mid term (HIV RNA <500 copies/mL, CD4+T cells <500/mm^3, AIDS events, non-AIDS events, death, and COS at year 3).

Odds ratios obtained for death at year 3 confirmed results of the multivariable logistic regression analysis when reasons and number of switches were not included. Patients with a CD4+ T cell count between 200 and 350/mm^3 vs. patients with <200 cells/mm^3 at baseline had a lower risk of death at year 3 (OR 0.40, 95% CI 0.26–0.63, p <0.0001). Older patients (OR 1.57, 95% CI 1.35–1.82, p <0.0001), patients with AIDS events at baseline (OR 1.73, 95% CI 1.25–2.38, p <0.0001), patients on DRV/r (OR 5.48, 95% CI 2.42–12.44, p <0.0001) and started on ATV/r (OR 2.96, 95% CI 1.78–4.93, p <0.0001) showed a greater risk of death at year 3. Patients who switched vs. patients who continued their regimen had an increased risk of death at year 3, especially those who switched for other/unknown reasons (OR 32.69, 95% CI 13.88–76.99, p <0.0001).

The same variables maintained their statistical significance for associations with COS at multivariable analysis. Results by anchor drug prescribed showed that patients started on LPV/r had an OR of 0.71 (95% CI 0.59–0.85, p 0.0003), and on DRV/r had an OR of 0.54 (95% CI 0.29–0.59, p 0.045) for COS at year 3

with respect to those treated with EFV. Probability of obtaining outstanding outcome decreased in patients who switched for virological failure (OR 0.36, 95% CI 0.24–0.55, p <0.0001). Number of switches was associated also with lower probability of reaching COS at year 3 (OR 0.89, 95% CI 0.85–0.93, p <0.0001) (Fig. 2).

Prediction performance of fitted models

Analysis of receiver operating characteristics was performed to estimate the best-fitting models to predict outcomes. Calculation of area under the receiver operating characteristics curve showed good performances of models applied in this study. In particular, COS at month 6 had an area under the curve of 0.87 (Fig. 3).

Discussion

This study evaluated clinical, virological, and immunological responses of HIV treatment in naïve patients starting a first-line HAART including either EFV or boosted PIs, at month 6 and at year 3. With this objective in mind, we defined a composite outcome of success (COS) and also weighted the individual components of this outcome.

In spite of reaching a good virological outcome (about 90% of the observed patients reached virological success at year 3), COS was reached in only a fraction (about 40%) of patients observed. Since any of the components of COS are significant for patients' health [17,18], it is important to study predictors for this kind of response.

One of the main variables studied as predictors was the anchor drug prescribed in the first-line regimen. Patients on EFV had a greater probability of reaching COS than patients on boosted PIs at year 3. Indeed, patients on LPV/r (the most frequently prescribed PI) had a greater risk of missing COS at year 3 than those on EFV. It is, however, important to consider that patients on PI/r were more advanced than those prescribed EFV. So, although these results were confirmed by the multivariable logistic regression analysis to adjust for imbalances at baseline, this comparison may suffer from a channelling bias. Moreover, it should be considered that period of follow-up is relatively short: longer periods of virological suppression may be needed to observe a comparable immune-reconstitution among the treatment groups. Nonetheless, if one assumes that initial virological suppression is a reliable surrogate marker for clinical success even at longer term, the results presented herein extend our previous observations [10] and seem to confirm trial results in clinical practice [2].

Perhaps the more outstanding finding was that patients prescribed ATV/r did not differ significantly from patients on EFV except for the mortality outcome (which may be more subjected to clinical conditions at baseline, however). The ACTG A5202 trial [19] did not reveal significant difference in terms of virological outcome for EFV compared to ATV/r. So, our results may be interpreted as a further clinical correlate for this finding [19], in line with reports of other observational cohorts [20], but in contrast to other evidence from clinical practice [21]. Also, the ACTG trial 5257, recently updated with results at week 96, showed that patients on ATV/r suffered from quite a significant risk of therapy discontinuations (e.g. 14% vs. 5% DRV/r) [14]. In our observational study, no significant differences in the rate of switching were observed between patients treated with ATV/r or with DRV/r. Also, the analysis of COS did not demonstrate any significant difference between ATV/r and EFV. So, conditions in real life may reduce the applicability of clinical trials to a significant extent. In particular, jaundice or its perception had a great impact on the risk of therapy discontinuation in the ACTG 5257 trial [14], while in clinical practice, high grade of hyperbilirubinemia and discontinuations for jaundice are not so frequent [22]. Altogether, our results underline the complexity

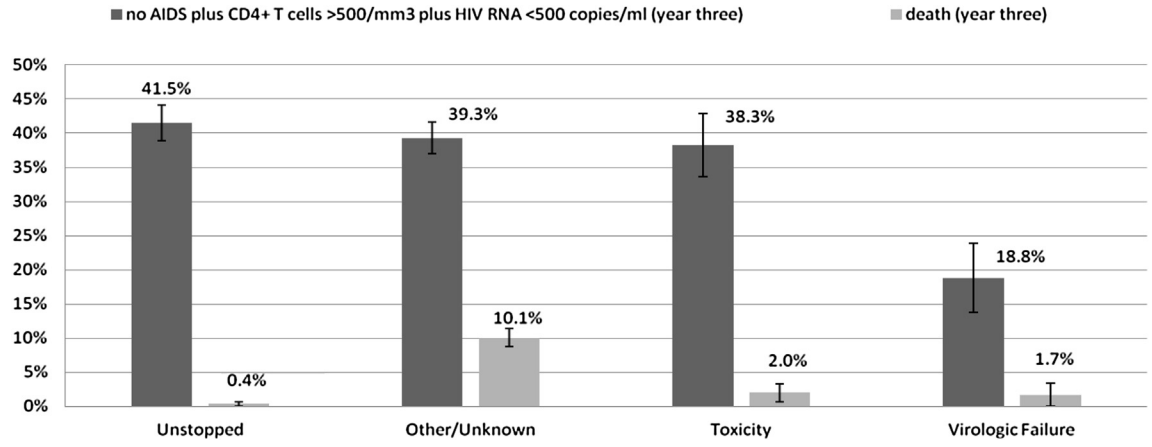

FIG. 2. Percentage of patients reaching the composite outcome for success at year 3 by switch occurred along the follow-up.

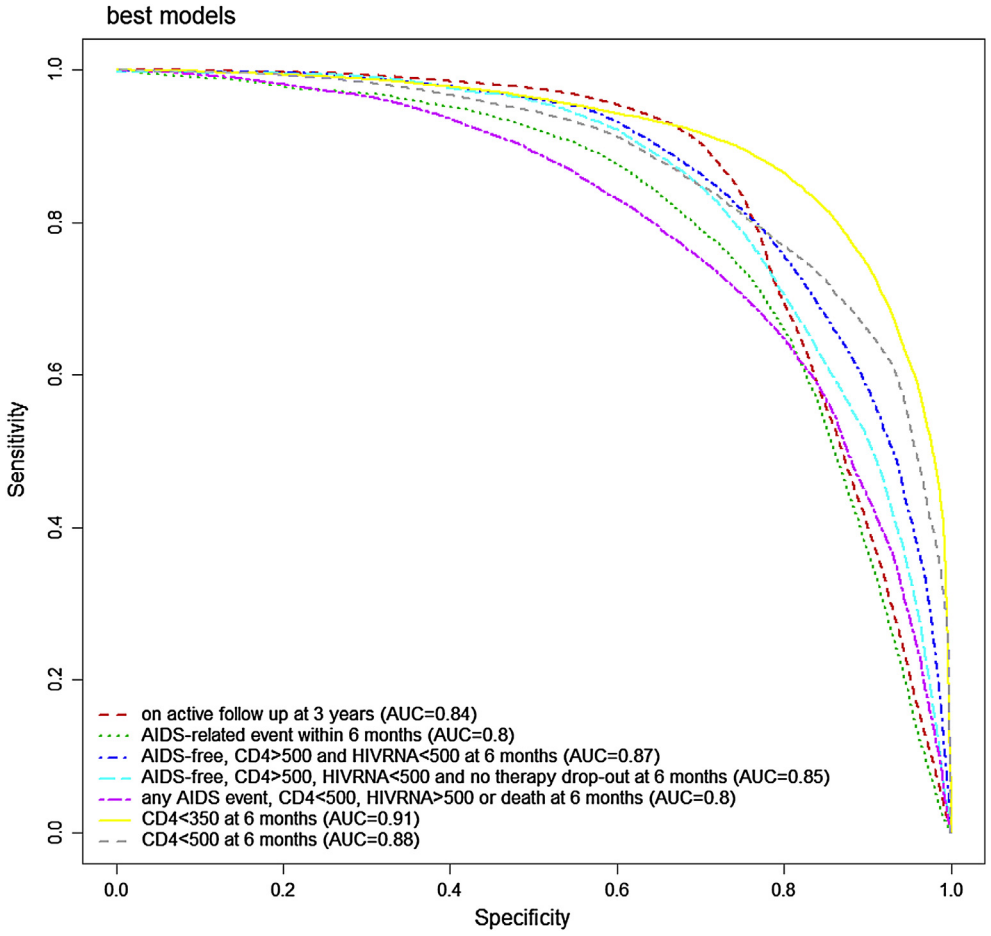

FIG. 3. Receiver operating characteristic (ROC) curves in cross-validation showing performances of best models (only those achieving an area under the ROC of 80% or more). AUC: area under the ROC curve.

of measuring the effect of treatment in clinical practice and interpret differences from clinical trials.

Interestingly, many patients switched off the initial anchor drug (>50% overall after 3 years), and the final outcome may not be referred to the first treatment choice. For this reason, we investigated the possible impact of number and reasons for therapy switches. Our study showed a lower probability of obtaining COS in patients who switched for virological failure vs. patients who switched for other reasons and in those who switched several times, but the switch did not appear to modify the impact of the remaining variables to a significant extent.

Foreign origin was significantly associated with worse outcomes (including COS), independently from possible confounders at baseline. A cohort study recently reported a so-called "healthy migrant effect," describing a lower mortality at year 4 in foreign patients vs. natives [23], although the same cohort reported higher incidence of AIDS (in particular, tuberculosis) in migrants during the first year of antiretroviral therapy [24]. In the Dutch cohort, foreign patients were less likely to achieve virological suppression and experienced more frequent diseases and death [25], even though other European cohorts did not report marked differences in AIDS, death, and access to therapy [26,27]. Although a multivariable analysis was performed, we cannot exclude that our results can be due to a greater proportion of foreign patients treated with less tolerable and more complicated regimens including boosted PI (especially the soft-gel LPV/r formulation) in the earlier 2000. In any case, our study suggests that attention should be paid to migrants who actually represent a significant proportion of those under care throughout Italy [28].

In this study, patients with positive HCV-Ab had a lower probability of reaching COS at year 3. By contrast, significant results were not observed in HBsAg carriers included in our study. The issue of differences in viro-immunological outcome after HAART is still unresolved [29,30]. However, when clinical outcomes are considered, HIV/HCV-co-infected patients showed a consistent increased risk of mortality for liver disease than HIV-mono-infected individuals [31].

This analysis may be affected by several limitations, being first the evaluation of observational data. In our case this may be relevant given the differences in the population strata (i.e. possible bias by indication). In any observational cohort study, it is impossible to exclude selection and/or channelling biases. Also, we studied only patients with available measures, so a "selection of the fit" effect could be present. Survival analyses were not performed because we were primarily interested in describing the outcome of observed patients at pre-defined time points, in analogy to previous analysis conducted by the same group [10]. However, consideration of outcomes variations, including also patients with partially available measures, confirmed the results of the main analysis (see Supplementary Materials). Lastly, specific adverse events or non-AIDS events were not evaluated. Non-AIDS events were only collectively evaluated, providing weak evidence of correlation with outcomes. Consideration of individual non-AIDS events would probably require a greater cohort of patients.

In conclusion, the present study showed that a good virological response was not coupled with COS compared to patients who received EFV, but not to those who received modern PI/r such as ATV/r. Patients at an advanced stage of the disease, of foreign origin, with positive HCV-Ab, and those who received a boosted PI (in particular LPV/r) in the first-line regimen, are at a greater risk of not achieving COS. So, optimization of HAART remains important, especially in the fragile populations of migrant patients who present late, and with HIV/HCV co-infection.

Transparency declaration

The authors declare no conflicts of interest. This work has been presented in part to the "6th Italian Conference on AIDS and Retroviruses" (Rome, 25–27 May 2014).

Acknowledgements

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2014.10.022

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